RESEARCH PLAN PROPOSAL

EFFECT OF BROCCOLI AND QUINOA AGAINST ANTIDEPRESSANTS INDUCED TOXICITY IN VITAL ORGANS IN SWISS ALBINO MALE MICE

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INTRODUCTION

Currently, depression is one of most significant major public health problems, and is a serious and common medical condition affecting physical health, mood, and thoughts. Major depression is characterized for symptoms at the psychological, behavioral and physiological levels (Yu *et al* 2011). It affects about 121 million people worldwide. World Health Organization (WHO) states that depression is the leading cause of disability as measured by Years Lived with Disability (YLDs) and the fourth leading contributor to the global burden of disease. By the year 2020, depression is projected to reach second place in the ranking of Disability Adjusted Life Years (DALY) calculated for all ages. Today, depression already is the second cause of DALYs in the age category 15-44 years.

An estimated 3-4% of India's 100 crore plus population suffers from major mental disorders and about 7-10% of the population suffers from minor depressive disorders.

Indians are among the world's most depressed country. According to a World Health Organization-sponsored study, while around 9% of people in India reported having an extended period of depression within their lifetime, nearly 36% suffered from what is called Major Depressive Episode (MDE).

A study based on the World Health Organization's World Mental Health Survey Initiative has said that India has the highest rate at 35.9 percent of major depression in the world. Figures from the health ministry suggest that women are twice as likely to suffer from depression that man.

Depression symptoms that the vast majority of people experience are caused by bad diet, lack of sleep, lack of exercise, alcohol, drugs, vitamin deficiencies, obesity, stress overload, disease, many toxins we are exposed to in everyday life and other social issues such as losing a loved one, divorce, loss of a job, low self esteem, family problem financial concerns, Genetic factors influence risk of illness and sensitivity to environmental factors and a family history of depression is also a risk factor for developing depression.

Antidepressants are classes of psychotherapeutic drugs that are used to treat major depression and other affective disorders. It takes about two weeks for the drugs to start working and about 6-9 months for the whole therapy or depend on the severity of illness as some people will need to take them longer. The antidepressant drug market reached sales of almost $11 billion in 2008. These are classified into 4 groups:

1. Serotonin reuptake inhibitors (SSRIs)
2. Serotonin norepinephrine reuptake inhibitors (SNRIs)
3. Tricyclic antidepressants (TCAs)
4. Monoamine oxidase inhibitors (MAOIs)

1. Serotonin reuptake inhibitors (SSRIs)

The SSRIs are the most commonly prescribed class of antidepressants and considered the first-line medications for the treatment of depression and anxiety. They act on a chemical in the brain called serotonin. The SSRIs include drugs such as Prozac, Zoloft and Paxil

2. Serotonin norepinephrine reuptake inhibitors (SNRIs)

SNRIs are the newest class of antidepressants. SNRIs work by increasing the levels of serotonin and nor epinephrine in the brain. The SNRIs include drugs such as Cymbalta and venlafaxine.

3. Tricyclic antidepressants (TCAs)

They are called "tricyclics" because there are three rings in the chemical structure.They work by inhibiting the brain's reuptake or serotonin and norepinephrine. They also partially inhibit the reabsorption of dopamine. The TCAs include drugs such as Amitriptyline and Clomipramine

4. Monoamine oxidase inhibitors (MAOIs)

MAOIs are the oldest class of antidepressants. MAOIs have severe interactions with certain foods, drinks, and medications. Combining MAO inhibitors with foods or drinks containing tyramine can result in dangerously high blood pressure, which can lead to a stroke or heart attack. Because of this danger, MAOIs are not typically chosen as a first-line depression treatment. The MAOIs include drug such as Phenelzine and Parnate.

Escitalopram is the most commonly prescribed antidepressant comprising 40% of the total prescriptions. This is followed by sertraline (17.6%) and fluoxetine (16.3%). In total, selective serotonin reuptake inhibitors (SSRIs) formed 79.2% of all the prescriptions. Tricyclic antidepressants formed a small part (15.15%) of total prescriptions with imipramine being the most commonly used tricyclic antidepressant. Serotonin-norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine and duloxetine) were prescribed to 11.3% of patients with equal share of venlafaxine and duloxetine. (Grover *et al* 2013*).*

MECHANISM OF ACTION:

The aim of an antidepressant is to stabilize and normalize the neurotransmitter in our brain Neurotransmitter such as serotonin; dopamine and norepinephrine play a role in a regulating mood. People with depression have lowered levels of serotonin. SSRIs block the reuptake of serotonin An SSRI binds to SERT ("serotonin transporter") and blocks its activity, allowing more serotonin to remain in the spaces between neurons and eases the symptoms of depression.

SSRIs inhibit the reuptake of serotonin. As a result, the serotonin stays in the synaptic gap longer than it normally would, and may repeatedly stimulate the receptors of the recipient cell. In the short run this leads to an increase in signaling across synapses in which serotonin serves as the primary neurotransmitter. On chronic dosing, the increased occupancy of pre-synaptic serotonin receptors signals the pre-synaptic neuron to synthesize and release less serotonin. Serotonin levels within the synapse drop, then rise again, ultimately leading to down-regulation of post-synaptic serotonin receptors. In summary, inhibition of serotonin reuptake increases serotonin concentration, which causes a down regulation of 5HT1A receptors. After the number of 5HT1A receptors is reduced, the neuron is disinhibited to release more serotonin in the synaptic space.

SNRIs MODE OF ACTION:

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a type of antidepressant medication that increases the levels of both serotonin and norepinephrine by inhibiting their reabsorption into cells in the brain. Although the precise mechanism of action isn't clear, it's thought that these increased levels enhance neurotransmission — the sending of nerve impulses — and thereby improves and elevate mood. Medications in this group of antidepressants are sometimes known as dual reuptake inhibitors

ANTIDEPRESSANT'S SIDE EFFECTS

The ability of the antidepressant to block neurotransmitters in the brain also causes some of the common adverse effects of these drug classes such as sexual dysfunction, weight gain, central nervous system (include increased anxiety, insomnia, sedation, nightmares, and headache), serotonin syndrome, hypertension and liver function tests. Adverse effects are the same but occur in varying degree with each drug in this group. Side effect of antidepressants can be predicted by receptor selectivity and site of action:

- Side effect by system – gastrointestinal, central nervous system and sexual dysfunctions.
- Sexual dysfunction is the most common side effect of all serotonin reuptake inhibitors. The stimulation of serotonin 5-HT2 and 5-HT3 receptors is a proposed mechanism for the occurrence of sexual dysfunction due to serotonin reuptake inhibitors, so it has been suggested that adding medications that block those receptors might help with this adverse effect (Khawam *et al* 2006).
- Nausea and vomiting are caused by stimulation of serotonin 3 receptors located at the hypothalamus and the brainstem.
- Effects on the GI tract are mediated stimulation of serotonin 3 and 4 receptors. This stimulation can lead to increased GI motility, GI cramps. If the increase in GI motility is severe enough this can lead to diarrhea.

- CNS side effects at the basal ganglia are mediated by 5HT2A receptor stimulation. Stimulation at the basal ganglia of these receptors can cause: Akathisia, Psychomotor retardation,Parkinsonism and Distonic movements

- Mental side effects are the second group of CNS side effects. Stimulation of 5HT2A and 5HTC receptors can lead to mental agitation, anxiety and panic attacks

Health issues such as high blood pressure, heart disease, diabetes, cancer, and depression can also be caused by an unhealthy dietary lifestyle. Super foods help to fight and prevent depression by increasing the levels of serotonin, a mood enhancing hormone in the brain without dangerous side effects of prescription medications. Super foods work by relieving stress and anxiety, invoking a positive mood, and helping to repair damage to neural pathways. These include- Whole grains, legumes and nuts, green tea, vegetables and fruits, protein-rich foods and seafood.

Whole grains:

Whole grains have been found to have calming effects and ease depressive symptoms because of their complex carbohydrates. Unlike simple kinds of carbohydrates, complex carbohydrates do not raise blood sugar that sparks off mood swings, fatigue, and overeating. These include whole grain such as amaranth, buckwheat, brown rice, corn, hulled barley, millet, **quinoa,** spelt, triticale, wild rice, whole rye, whole wheat berries, whole wheat bulgur, and whole cornmeal.

Vegetables and fruits:

Fruits and vegetables are high in antioxidants that fight free radicals. These free radicals are responsible for stopping our body organs, including the brain, from doing its normal functions. Vegetables and fruits are first-rate sources of antioxidants, including Vitamins A, C, and E. They help limit the negative effects of free radicals to the brain, which suffers a lot during bouts of depression. These include vegetables and fruits such as green leafy vegetables, colorful vegetables, berries, orange, apricot and **broccoli.**

Superfood is a marketing term used to describe foods with supposed health benefits and refers to foods that are low in calories and high in nutrients. It is powerful enough to help lower cholesterol, reduce risk of heart disease cancer and neurodegenerative disorders. This function is largely due to the antioxidant effects of their bioactive component. These include:

1. Broccoli (*Brassica oleracea var.italica)*:

Broccoli is a green vegetable and mainly consumed for its floret. Broccoli is a source of bioactive compounds such as phenolics, flavonoids and glucosinolates and sulforaphane which possess antioxidant and anticancer effects. Apart from other nutritional antioxidants, broccoli is also a significant source of calcium, folic acid, carotenoids, ascorbic acid and known to reduce risk of breast and prostate cancer.

Nutrient and antioxidants may act together to reduce reactive oxygen species level more effectively than single dietary antioxidant, because they can function as synergists.

HEALTH BENEFITS OF BROCCOLI:

- **Nervous System**: high amount of potassium maintain a healthy nervous system and optimal brain function, as well as promotes regular muscle growth.
- **Blood Pressure**: it has high amount of potassium and also contains magnesium and calcium that help regulate blood pressure.
- **Vitamin C**: vitamin C and an antioxidant necessary for fighting against free radicals. It is an effective antihistamine for easing the discomfort of the common cold.
- **Bone Health**: it contains both calcium and vitamin K which are important for bone health and prevention of osteoporosis.
- **Sun Damage**: It contains glucoraphanin which helps the skin to detoxify and repair itself.
- **Immune System**: Beta-carotene and Trace minerals, such as zinc and selenium which act to strengthen immune defense actions.
- **Cancer Prevention**: It contains glucoraphanin, which with the body processes into the anti-cancer compound sulforaphane. It also contains indole-3-carbinol, a powerful antioxidant compound and anti-carcinogen found to not only hinders the growth of breast, cervical and prostate cancer, but also boosts liver function.
- **Eye Health**: it contains carotenoid lutein helps prevent cataracts, as well as possesses anti-cancer effects and also good source of vitamin A that is needed to form retinal and the light-absorbing molecule that is essential for both low-light and color vision.
- **Heart Health**: The carotenoid lutein may also slow down or prevent the thickening of arteries in the human body, thus fighting against heart disease and stroke. The B6 and folate in broccoli also reduce the risk of atherosclerosis, heart attack, and strok.

2. Quinoa (*Chenopodium quinoa Willd.)*:

Quinoa is a pseudocereal native to the Andean regions of South America since 3000 b.c. It was called ‘‘the mother grain’’ by the Incas. Chenopodium quinoa is being considered as a new crop

for the Controlled Ecological Life Support System (CELSS) because of its high protein values (12-18%) and unique amino acid composition. Lysine, an essential amino acid that is deficient in many grain crops, is found in quinoa. It is an important source of minerals and vitamins and contains significant amounts of antioxidant phytochemicals including: flavonoids, phenolic acids, fat soluble vitamins, fatty acids, trace elements and squalene and also a gluten free grain. Besides, it has been considered an oil crop, with an interesting proportion of omega-6 and notable vitamin E content.

HEALTH BENEFITS OF QUINOA:

- **Protein-rich food**: It is complete protein containing all nine essential amino acids.
- **Contains fiber:** It relieve constipation and helps to prevent heart disease by reducing high blood pressure and diabetes. Fibers lower cholesterol and glucose levels and may lower risk of developing hemorrhoids and help to lose weight.
- **Contains Iron:** It helps keep red blood cells healthy and hemoglobin formation and carries oxygen from one cell to another and supplies oxygen to muscles to aid in their contraction and increases brain function. It also benefit in neurotransmitter synthesis, regulation of body temperature, aids enzyme activity and energy metabolism.
- **Contains lysine:** It is essential for tissue growth and repair.
- **Rich in magnesium:** It helps to relax blood vessels and alleviate migraines. It reduces Type 2 diabetes by promoting healthy blood sugar control and also include in transmission of nerve impulses, body temperature regulation, detoxification, energy production, and the formation of healthy bones and teeth.
- **High in Riboflavin (B2):** It improves energy metabolism within brain and muscle cells.
- **High content of manganese:** It is an antioxidant which helps to prevent damage of mitochondria during energy production as well as to protect red blood cells and other cells from injury by free radical.
- **Gluten-free:** It is not related to wheat or even a grain, it is gluten-free. It is useful in Celiac disease or gluten intolerance.

Antioxidants are the molecules that help to protect cells from the damaging physiological process known as oxidative stress. Reactive oxygen species such as superoxide, hydroxyl and peroxyl radicals play an important role in oxidative stress which is related to the pathogenesis of different diseases such as inflammatory disorders, cataracts and various cancers. There has been growing demand for antioxidants due to their defensive role against free radical toxicity in our body systems.

The most common natural antioxidants are flavonoids and phenolic acids which are present in fruits and vegetables. They are not only the defensive molecules in prevention of different pathological disorders but are commonly used in industry for the prevention of oxidative degradation of polymers and synthetic and natural pigments. Radicals have been proposed to induce cellular damage which may play a role in heart disease, rheumatoid arthritis, cancer and inflammatory disorders as well as in aging processes.

OBJECTIVES

- **Observe the toxicity in vital organs caused by continuous use of antidepressants.**
- **To study the effects of Broccoli and Quinoa by assessing various biochemical parameters and hormonal level**
- **Histopathological study of different tissue in Swiss albino male mice**

REVIEW OF LITERATURE:

Ismail and Dar *(*2009) studied the comparison of the efficacy of floxentine, phenelzine and moclobemide in rodents using animal models of depression and suggested that animal models of depression such as forced swimming test and tail suspension test are useful tools for the assessment of potential antidepressants. The duration of the immobility time in both tests is reduced after pretreatment with a variety of antidepressants.

Ebuehi *et al* (2013) observed that oral administration of Sertraline and Clozapine affects Memory, Liver Enzymes and Function in Rats and they observed that the blood chemistry and liver function show significant increase in activities of ALP, AST and ALT between drugs administered groups and control. Thus they concluded that elevated activities of liver enzymes,

AST and AST indicate impairment of liver function in rats orally administered clozapine and sertraline in rats.

Brain and liver oxidative stress after sertraline and haloperidol treatment in mice was studied by Abdel-Salam *et al* (2013) and they observed that the Haloperidol is a classic antipsychotic drug known for its propensity to cause extrapyramidal side effects and Sertraline is an antidepressant drug which has been reported to cause extrapyramidal symptoms.Treatment with sertraline worsen the effect of haloperidol on oxidative stress in the brains of mice.

Oxidative Tissue Damage Induced by Citalopram in Rat Different Organs was studied by Abdelmajeed (2009). He observed that citalopram produced significant increase in the activity of free radical producing enzyme, xanthin oxidase (XO), with concomitant elevated level of nitric oxide (NO) in liver, kidney and heart as compared with normal animals, implying oxidative tissue damage. The alteration of such biomarkers was parallel with increased malondialdehyde (MDA), index of lipid peroxidation) in kidney, and decreased in adenosine triphosphatase (ATPase) and lactate dehdrogenase (LDH) activities in cardiac tissue. The oxidative tissue damage induced in liver in response to citalopram ingestion was ensured by a reduction in the activity of liver sorbitol dehydrogenase (SD) with concomitant elevation in liver serum marker enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) and also the increase of serum markers of kidney, creatinine and uric acid levels as well as in serum biomarker enzyme of heart, creatinephosphokinase (CPK) in citalopram treated animals versus normal ones, indicating the adverse toxic effects of the used drug on kidney and heart tissues.

AL-Howiriny (2008) studied the evalution of hepatoprotective activity of broccoli '*Brassica oleracea* ' in rats and he observed that ccl4 induced hepatotoxicity in all treated animals and found elevated serum level of GOT , GPT, ALP,GGT and bilirubin levels and fall in NP-SH and increased MDA activities in liver tissue. The broccoli extract produced hepatoprotection by decreasing the activity of serum enzume,bilirubin, increased NP-SH levels and decreased MDA of liver tissue.

Effect of diet supplemented with quinoa seeds on oxidative status in plasma and selected tissues of high fructose-fed rats was studied by Pasko *et al* (2010). They concluded that quinoa seed influenced the oxidative stress as was evidenced by decreasing MDA in plasma and decreasing the activities of antioxidant enzyme (eSOD,CAT,pGPX). Quinoa seed can act as a moderate protective agent against potential of fructose-induced changes in rats by reducing lipid peroxidation and by enhancing the antioxidant capacity of blood and heart, kidney, testis, lung and pancreas.

Hepatoprotectivite activity of *Brassica oleracea* L. var. *Italica* was studied by Hashem *et al* (2013). They observed that broccoli extracts have prophylactic activity against liver damage induced by paracetamol in rats. Phytochemical investigation of 80% ethanolic extract resulted in

isolation of three compounds; obtucarbamate, N-(4-hydroxy phenyl) acetamide and p-hydroxy benzoic acid which helps in the protection of liver damage.

Protective effects of quercetin on liver injury induced by ethanol was studied by Chen (2010) They observed that the rats that were orally treated with 50% ethanol for continuous ten days, which resulted in cell necrosis, fibrosis and inflammatory infiltration and concluded that by preventive and synchronism treatment with quercetin for fourteen days, the contents of AST, ALT ADH, γ-GT, TG and MDA, and levels of IL-1β, IL-1, IL-6, IL-8, and TNF-α were significantly reduced, whereas GSH and level of IL-10 were obviously increased. It may be deduced that quercetin, by multiple mechanisms interplay, demonstrated protective effect on liver injury induced by ethanol in rats

Protective effect of quercetin against gentamicin-induced nephrotoxicity in rats was studied by Abdel *et al* (2009) .They observed that BUN and serum creatinine levels were significantly increased. The significant decrease in GSH levels, superoxide dismutase (SOD), CAT activities and increase in lipid peroxide (TBARS) levels, indicated that GM-induced nephrotoxicity was mediated through oxidative stress reactions. Histopathological examination of GM-treated rats revealed degenerative changes in glomeruli and tubules. And concluded that simultaneous administration of quercetin plus gentamicin protected kidney tissues against nephrotoxic effects of gentamicin as evidenced from amelioration of histopathological changes and normalization of kidney biochemical parameters.

Jahromy and Moghadam (2014) studied the effects of sertraline on sperm motility, number and viability and its relation to blood levels of testosterone, FSH and LH in adult male mice and they observed that the viability, count and motility of sperms were decreased. Testosterone level of blood was also decreased while FSH was increased. There was no significant change in LH level. It is suggested that Sertraline at higher dose decreases sperm production and has the potential to affect adversely fertility in male mice.

MATERIALS AND METHODS

ANIMALS:

Male Swiss albino mice weighing between 20 and 30 g will be used. The animals will be housed under standard laboratory conditions and maintained on natural light and dark cycle and will have free access to food and water. Animals will be adapted to laboratory conditions before the experiment. Each group will have minimum seven animals.

BEHAVIORAL TEST FOR DEPRESSION

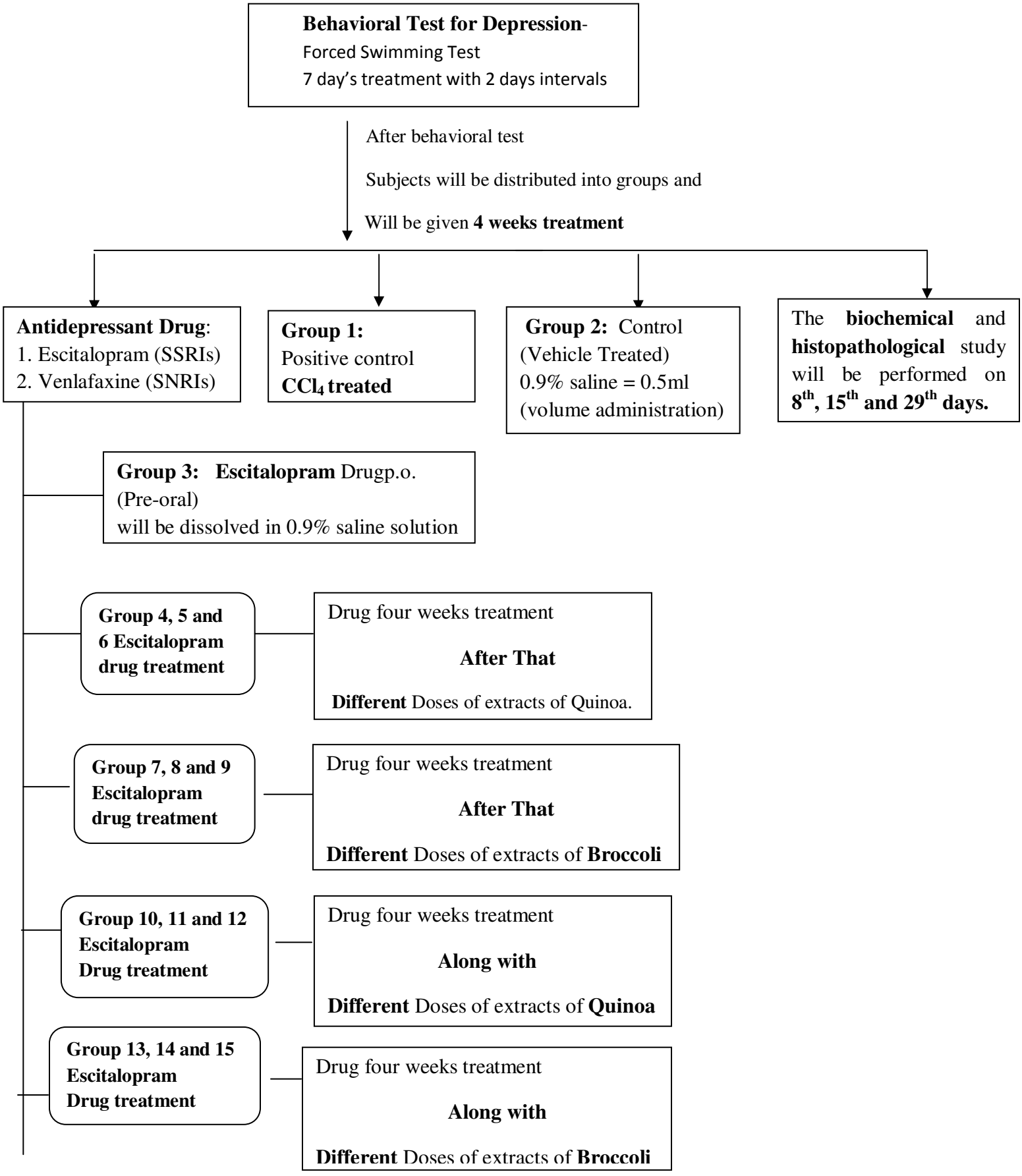
FORCED SWIMMING TEST (FST): MEASUREMENT OF IMMOBILITY PERIOD

Mice will be dropped individually into glass cylinders (height: 25 cm; diameter: 10 cm) containing 10 cm water, maintained at 25±1 ºC, and remained there for 6 min. A mouse will be judged to be immobile when it floated in an upright position and made only small movements to keep its head above water and the time of immobility will be recorded during the last 4 min of the 6-min testing period, thus after 2 min of habituation (Chenu *et al* 2006) .Results will be expressed as the immobility time during the 240-s test period (mean±S.E.M.) for the 7 mice tested in each group.

Two different classes of antidepressents will be used in the study

1. **SSRI –** In this class we will use drug Escitalopram
2. **SNRI-** In this class we will use drug Venlafaxine

PLAN OF WORK:


Behavioral Test for Depression-
Forced Swimming Test
7 day's treatment with 2 days intervals
After behavioral test
Subjects will be distributed into groups and
Will be given 4 weeks treatment
Antidepressant Drug:
1. Escitalopram (SSRIs)
2. Venlafaxine (SNRIs)
Group 1:
Positive control
CCl4 treated
Group 2: Control
(Vehicle Treated)
0.9% saline = 0.5ml
(volume administration)
The biochemical and histopathological study will be performed on 8th, 15th and 29th days.
Group 3: Escitalopram Drugp.o.
(Pre-oral)
will be dissolved in 0.9% saline solution
Group 4, 5 and 6 Escitalopram drug treatment
Drug four weeks treatment
After That
Different Doses of extracts of Quinoa.
Group 7, 8 and 9 Escitalopram drug treatment
Drug four weeks treatment
After That
Different Doses of extracts of Broccoli
Group 10, 11 and 12 Escitalopram Drug treatment
Drug four weeks treatment
Along with
Different Doses of extracts of Quinoa
Group 13, 14 and 15 Escitalopram Drug treatment
Drug four weeks treatment
Along with
Different Doses of extracts of Broccoli

Group 16: Venlafaxine Drug
p.o. (Pre-oral)
will be dissolved in 0.9% saline solution

Group 17, 18 and 19
Venlafaxine
Drug treatment

Drug four weeks treatment

After That Different
Doses of extracts of **Quinoa**.

Group 20, 21 and 22
Venlafaxine
Drug treatment

Drug four weeks treatment

After That Different
Doses of extracts of **Broccoli**

Group 23, 24 and 25
Venlafaxine
Drug treatment

Drug four weeks treatment

Along with

Different Doses of extracts of **Quinoa**

Group 26, 27 and 28
Venlafaxine
Drug treatment

Drug four weeks treatment

Along with

Different Doses of extracts of **Broccoli**

PARAMETERS

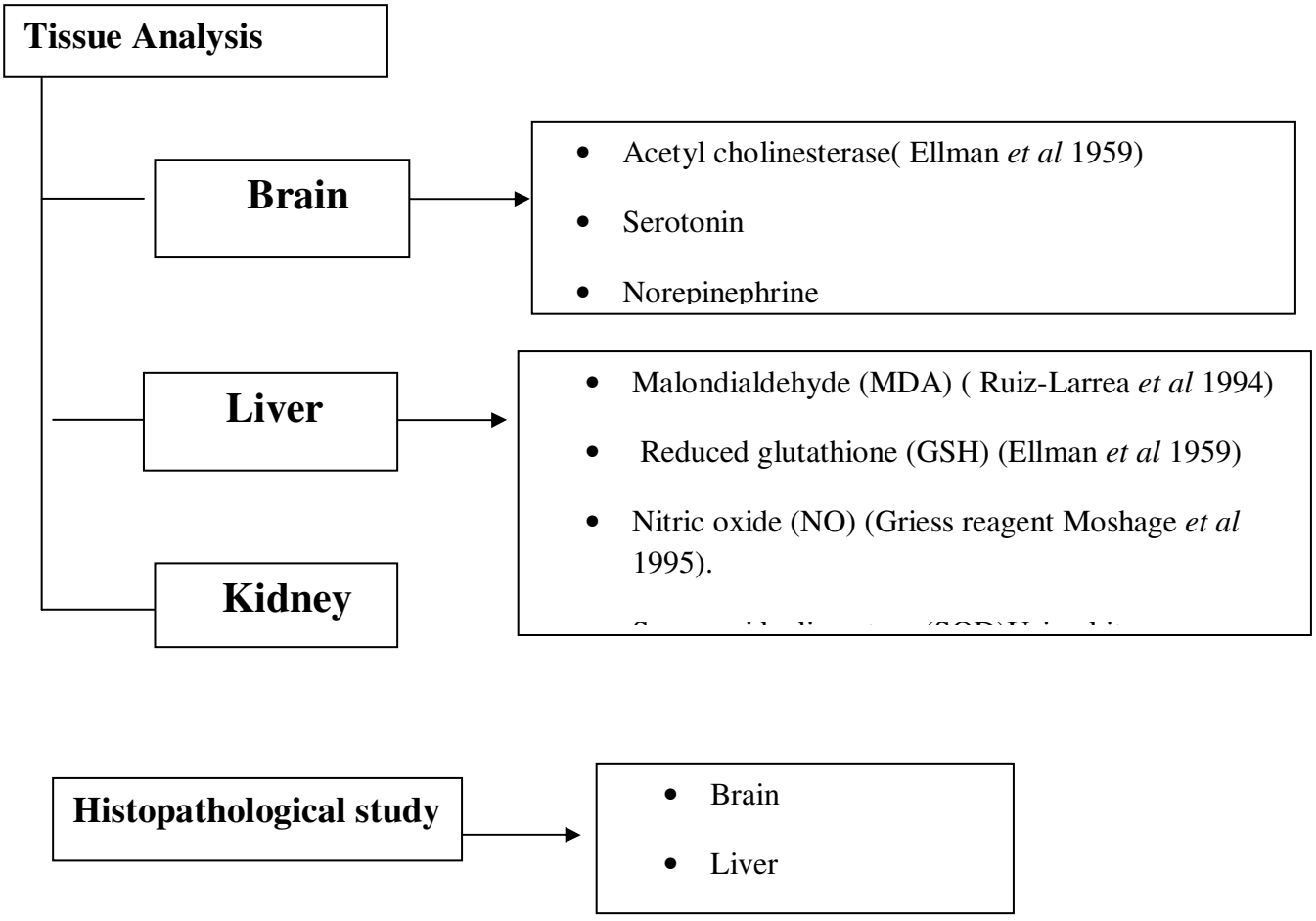
Biochemical Assessments:

Biochemistry test →

- Alkaline Phosphatase
- ALT (Alanine aminotransferase)
- AST (Aspartate aminotransferase)
- Bilirubin
- BUN (Blood urea nitrogen)
- Calcium
- Creatinine
- Glucose
- Phosphorus
- Total Protein
- Sodium
- Potassium
- Chloride

Hormonal Assay Test →

- Serum luteinizing hormone (LH),
- Follicle stimulating hormone(FSH),
- Testosterone concentrations (Enzyme linked immunosorbant assay (ELIZA) kits, BioCheck,



Statistical analysis:

The data will be expressed as Mean ± S.E.M. (Standard error mean). The statistical significance between groups will be analyzed using‘t’ test.

SIGNIFICANCE

Continuous use of antidepressants causes various side effects. Broccoli being rich in calcium, folate, fiber, and vitamins A, C, K, E and B and antioxidants. It contains sulforaphane and indol 3 carbinol which boost many antioxidant enzyme and biomarker enzymes.Quinoa considered pseudograin has remarkable nutritional properties; not only from its protein content (15%) but also from its great amino acid balance. It is an important source of minerals and vitamins, and has also been found to contain compounds like polyphenols, phytosterols, and flavonoids with possible nutraceutical benefits.

Since both Broccoli and Quinoa contain antioxidants our study may support that Broccoli and Quinoa intake may have a protective effect against antidepressant drugs induced oxidative damage

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